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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,417	01/07/2002	Michele Pagano	5914-090-999	1343

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
02/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/042,417	PAGANO, MICHELE	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,7-9 and 22-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3, 7-9 and 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 16, 2007 has been entered.

Claims 1-3, 7 and 23-26 have been amended. Claims 27-33 have been added. Claims 1-3, 7-9 and 22-33 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-9, 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 28 are vague in the recitation of "with or without phosphothreonine at position 8". It is unclear if this statement is intended to encompass amino acids sequence absent the phosphothreonine residue such that the sequence includes NAGSVEWPKKPGLRRRQT, of if applicant intends to claim the method wherein SEQ ID NO:91 is both phosphorylated or non-phosphorylated on the threonine of position 8. For purpose of examination, the claim will be read as requiring SEQ ID NO:91 having a phosphothreonine or a threonine at position 8. Amendment of the claims to recite "with or without phosphorylation of threonine at position 8" would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 7 have been amended to incorporate the limitation "wherein a purified or partially purified Cks1 is added to the reaction mixture". The instant specification described the addition of a purified or partially purified Cks1 to the reaction mixture in a method of determining the effect of the Cks1. The specification does not describe a screening method for compounds useful for the treatment of proliferative and differentiative disorder comprising the separate addition of Cks1 as a purified or partially purified substance. One of skill in the art would reasonably conclude that applicant was not in possession of the invention at the time of filing.

Claims 1-3, 7-9 and 22-33 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for compounds which are candidates for the treatment of proliferative and differentiative disorders, does not reasonably provide enablement for a method for screening for compounds which are useful for the treatment of proliferative and differentiative disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to methods for screening compounds based on perturbing the interaction of skp2, p27, Cdk2 and cks1, and the result of said perturbation on the ubiquitination of p27, or the perturbation of the ubiquitin ligase activity of skp2, based on the interaction of skp2 with cks1.

Carrano et al teach that Skp2 is required for ubiquitin mediate degradation of p27. Carrano et al teach that in many cancer cell lines, Skp2 levels are high and that a specific small-molecule inhibitor of Skp2 should increase the cellular abundance of p27 and lead to a block in cellular proliferation and disease progression (page 198, last paragraph). However, not all small molecules which modulate the interaction of skp2 and cks1, or molecules inhibiting the ubiquitin

ligase activity of skp2 would be suitable for the treatment of proliferative and differentiative disorders.

Mohanlal WO 02/40717, page 1, lines 12-26) teaches

An important reason for the high failure rate in clinical trials is the poor predictive value of currently used screening technologies for biological validation, pharmacological testing, and screening for success or failure of chemical entities and biologicals in clinical trials involving human subjects. These screening technologies are based on in vitro cell-based screening models and in vivo animal models, which often lack or inadequately represent the clinical disease phenotype of the patients in which the tested chemical entities or biologicals are intended to be used in the future. Therefore, success of these chemical entities or biologicals in these models does not necessarily translate into clinical success in patients. Hence, the majority of chemical entities or biologicals, while successful in these preceding screening and animal models, fail in clinical trials, particularly in late phase II and phase III trials(38). It has been estimated that more than 90% of new chemical entities(NCEs) fail in clinical trials, of which approximately two third fail for pharmacodynamic reasons (lack of efficacy and/or an unacceptable adverse event profile); the remaining third fail for pharmacokinetic reasons (3).

In the instant case, the screening methods of the specification provide for candidate compounds for further testing, but until said compounds demonstrate satisfactory pharmacodynamics in vivo and have been tested for un acceptable adverse events, one of skill in the art could not use said compounds directly as claimed for the treatment of proliferative and differentiative disorders.. Amendment of the claims to specify that the screening method provides candidate compounds for the potential treatment of proliferative and differentiative disorders would overcome this rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 , 22, 25, 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (U.S. 5,981,702, reference AD of the IDS filed April 22, 2002) in view of Carrano et al (Nature Cell Biology, August 1999, Vol. 1, pp. 193-199, cited in a previous action).

Claim 1 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorder comprising contacting a test compound with a reaction mixture comprising Skp2, p27 and Cdk2, wherein a purified or partially purified CKS1 is added to the reaction mixture, and detecting a change in Skp2 binding activity or Skp22 ubiquitin ligase activity, wherein a change in the binding or ubiquitin ligase activity of Skp2 is detected , then a compound is useful for the treatment of proliferative or differentiative disorders is identified. Claim 2 embodies the method of claim 1 wherein the change in Skp2 binding activity is detected by a change in the binding of Skp2 with p21. Claim 3 embodies the method of clam 1 wherein the change in the Skp2 ubiquitin ligase activity is detected by detecting change in the ubiquitination or degradation of p27. Claim 22 embodies the method of claim 1 wherein said CKS1 is purified from an recombinant expression system. Claims 25 and 26 embody the method of claim 2 wherein an increase in the binding of Skp2 to p27 is detected and a decrease in the binding of Skp2 to p27 is detected, respectively.

Zhang et al teach that cycA/CDK2/p45/p19 and p9 exist as a complex. Zhang et al teach that p45 is a Skp polypeptide which is commensurate with the Skp2 polypeptide (column 44, lines 21-25). Zhang et al teach that the biological activity of p45 polypeptides is the ability of p45 to bind a complex of cycA/CDK2, p19 and p9, wherein p9 is either of CKS1 or CKS2 (column 3, lines 49-52). Zhang et al teach that agents which can disrupt the function of normal Skp from binding to cyclin-dependent kinases or to other CDK-associated proteins can be useful therapeutically to alter the growth and/or differentiation of a cell (column 7, lines 43-55). Zhang et al teach reconstitution experiments using recombinant p45/p19/cycA/CDK2 (column 44, lines 26-39) and conclude that p9(CKS1) or p9(CKS2) are capable of joining cycA/CDK2 with or without p45 (column 44, lines 40-49). Zhang et al teach that cycA, CDK2, p19, p45 and p9 are

the major p45 associated proteins in human cells (column 44, lines 61-64). Zhang et al teach that cycA complexes containing p19 and p45 are much more abundant in transformed cells than in normal cells (column 48, lines 63-65). Zhang et al do not teach the interaction between a complex comprising cycA/CDK2/p45/p19/p9 and p27/Kip1.

Carrano et al teach that Skp2 is required for ubiquitin mediate degradation of p27. Carrano et al teach that in many cancer cell lines, Spk2 levels are high, and that a specific small-molecule inhibitor of Skp2 should increase the cellular abundance of p27 and lead to a block in cellular proliferation and disease progression (page 198, last paragraph). Carrano et al teach that Skp2 interacts physically with phosphorylated p27 in vitro and in vivo (page 194, under "Results"). Carrano et al suggest that during S and G2 phase levels of p27 are kept low by increased levels of Skp2 and cycA/CDK2 (page 198, second column, lines 11-13).

It would have been prima facie obvious at the time that the claimed invention was made to provide a reconstituted complex of cycA/CDK2/p45/p19 and p9(CKS1 or CKS2) and p27(Kip1) and subject said reconstituted complex and p27(Kip1) to screen for specific small molecule inhibitors of Skp2, wherein an alteration of the interaction of Skp2 with p27 is measured by the change in binding to p27 or a change in the ubiquitination or degradation of p27. One of skill in the art would have been motivated to do so by the teachings of Carrano et al on the requirement for cycA/CDK2 and Shp2 for p27 ubiquitination and degradation and the teachings of Zhang et al on the complex of Shp2(p45) which binds to a complex of cycA/CDK2, p19 and p9.

All claims are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643